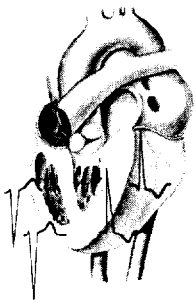


The Treatment of Mild Hypertension

Since almost 1 in 10 adults exhibits slight but persistent elevation of blood pressure, mild hypertension probably represents the most common—and most difficult—chronic disease that the family physician has to deal with. So says this world authority on the subject, who goes on to say that he has little confidence in diet as a control mechanism in the disease.

Edward D. Freis, M. D.
Senior Medical Investigator
Veterans Administration Hospital
Washington, D. C.

► While there is no general agreement as to a precise definition of mild hypertension, this discussion will include all patients who exhibit a diastolic blood pressure of 90 to 105 mm Hg (average of several office visits). Hypertension should not be diagnosed without a minimum of three separate office or clinic visits. Recent experience with community screening programs indicates that a high proportion—between 40 and 60%—



At the other end of the spectrum is the black male who develops hypertension before the age of 35. His risk of premature death is very high.

of those found to be hypertensive on the initial examination will be normotensive on subsequent testing. Such individuals are better defined as borderline hypertensives rather than mild hypertensives. Some will go on to develop a persistent hypertension in future years while others will remain normotensive on long term followup. The borderline cases are best left untreated although they should be reexamined periodically to detect those who progress to a definite, persistent hypertension. In this discussion we will be concerned with the treatment of mild but persistent hypertension.

Approximately 23 million persons in the United States exhibit a blood pressure of 160/95 mm Hg and at least 15 million more exhibit either a systolic of 140-159 or a diastolic of 90-94 mm Hg. It can be conservatively estimated that 30 million persons will exhibit mild hypertension on a single examination and that 60% of these or 18 million will remain mildly hypertensive on subsequent examinations. Therefore, since almost 1 in 10 adults exhibits persistent although slight elevation of blood pressure, mild hypertension probably represents the most common chronic disease that the family physician has to deal with.

Unlike other common chronic disorders such as arthritis, hypertension presents no symptoms. Patients feel well until they are struck down by one of the major complications. For the conscientious physician who wishes to practice preventive medicine, hy-

pertension is one of the most difficult therapeutic problems to deal with. Patients are not motivated to accept treatment when they feel well and are not very willing to endure side effects when these occur. There is, in addition, the expense and inconvenience of periodic visits to the physician's office and of medications. Since treatment, once begun, generally is life-long, the physician must consider carefully the need for therapy before initiating a long term program.

Before making such an important therapeutic decision we should ask ourselves what is the evidence that treatment is effective in preventing the complications of mild hypertension? Thus far, the only well controlled trial which included patients with mild hypertension is the Veterans Administration Cooperative Study on Antihypertensive Agents. This study included 523 male patients whose diastolic pressures averaged between 90 and 129 mm Hg over two to four clinic visits. The reliability of these patients with respect to taking medications was carefully checked before including them in the study. They were then randomly assigned double-blind to a combination tablet of hydrochlorothiazide 50 mg and reserpine 0.1 mg given twice daily, as well as hydralazine 25 to 50 mg three times daily, or else to placebos of these tablets. This combination was highly effective in reducing the blood pressure in the majority of these patients.

Although the plan was to follow both groups of patients, the treated and the untreated, for a period of five years, the study was discontinued in the subgroup of 143

From the Veterans Administration Hospital and the Department of Medicine, Georgetown University, Washington, D. C.

patients with initial diastolic blood pressures of 115-129 mm Hg after an average followup of only 18 months. During that period, 27 of 70 patients in the control group developed major complications, of which four were fatal. Prominent among these complications were the appearance of pre-malignant or malignant hypertension, stroke, congestive heart failure, dissecting aortic aneurysm and renal damage. By contrast, only one of the 73 treated patients developed a complication—a mild stroke from which the patient made a good recovery.

There remained in the study 380 patients with mild and moderate hypertension, that is, initial diastolic blood pressures averaging in the range of 90-114 mm Hg. These patients were observed for an average period of 3.3 years, although some were followed for longer than five years. Life-table analysis of the results indicated that 56% of control patients would be expected to develop major complications over a five-year period, as opposed to only 18% of the control group—a three to one difference. There were 19 deaths due to cardiovascular causes in the control group as compared to eight in the treated patients, a greater than 2 to 1 difference. In addition, there were 20 patients, all in the control group, whose diastolic blood pressures rose to 125 mm Hg who were removed from the trial only because of the elevated blood pressure.

Treatment appeared to have a greater influence on preventing strictly "hypertensive" complications such as hemorrhagic stroke, congestive heart failure, renal damage, dissecting aneurysm and malignant

phase of hypertension than on atherosclerotic complications such as myocardial infarction and sudden death. In fact, the incidence of myocardial infarction was the same in the control and treated groups, although the incidence of fatal attacks was somewhat higher in the former.

Who Benefited Most?

When the patients were divided into two subgroups of mild (90-104 mm Hg) and moderate (105-114 mm Hg) prerandomization-average-diastolic-blood-pressure, it became apparent that the major therapeutic benefit was obtained in the moderate group. In this group the difference in the incidence of morbidity between the control and treated group was 4 to 1, whereas in the mild group it was less than 2 to 1.

The majority of the complications in the treated patients with mild hypertension were due to myocardial infarction and other manifestation of coronary artery disease such as atrial fibrillation and second or third-degree heart block. As indicated above, treatment appears to have less effect on preventing the progress of atherosclerotic complications. However, such complications are the very ones that are most apt to occur in mild hypertension. Unless the disorder advances to a more severe stage, the patient with mild hypertension never develops malignant phase, renal failure or dissecting aneurysm, and seldom develops hemorrhagic stroke in comparison to the patients with more severe hypertension. Patients with mild hypertension are most likely to develop the complications associated with coronary artery disease or ather-

othrombotic cerebrovascular disease, or possibly congestive heart failure.

Another possible reason for failing to observe greater benefit from antihypertensive drug treatment in mild hypertension in the VA study was the relatively short period of observation. The natural history of mild hypertension is much longer than in the more severe forms of hypertension. The time span from the appearance of the hypertension to the incidence of major cardiovascular complications is usually 20 to 30 years or longer. Furthermore, the average age of the patients in the Veterans study was 49 years and one-fifth were over the age of 60 years. The average duration of known hypertension was five years. Therefore, many patients probably already had severely atherosclerotic coronary arteries which could not be reversed by antihypertensive drug treatment. Thus, the Veterans study left unanswered the question of whether prolonged treatment of mild hypertension, beginning in the early stages, will prevent the accelerated and aggravated atherosclerosis of the coronary arteries that such patients are so prone to develop. Long term controlled trials on the effectiveness of treatment in mild hypertension are presently underway, but it will be many years before definitive answers will be forthcoming.

Because of the above considerations, the physician in dealing with a patient with mild hypertension needs to take into consideration other factors than just the blood pressure. These risk factors include the following:

- **Age, Sex and Race**—It has long been known from life insurance statistics that

men aged 35 to 45 with mild hypertension have a greater reduction in normal life expectancy than similarly hypertensive men aged 55 to 65 years. It is also known that when hypertension appears at a young age it has a greater tendency to progress to a more severe stage of the disease than is the case with older patients.

Age-adjusted mortality rates are higher in men with hypertension than in women, the difference being 1½ to 1 times higher in men. The racial difference is even more marked. Death rates from hypertensive cardiovascular disease have been reported to be four to six times higher in blacks of both sexes as compared to whites in studies carried out in Charleston, S.C. and Chicago. Vital statistics indicate that deaths from cerebrovascular diseases in blacks, which are often associated with hypertension, are nearly twice those of whites in both sexes.

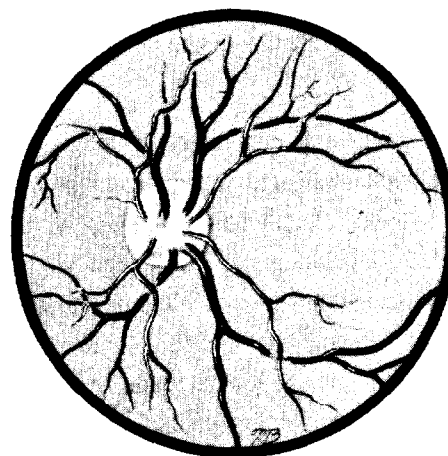
Age, race and sex are simple indices that are very useful in arriving at an estimate of prognosis. At one end of the spectrum are white females aged 60 or above with mild hypertension. Their mortality rates are little, if any, higher than for normotensive females of the same age. At the other end of the spectrum is the black male who develops hypertension before the age of 35. His risk of premature death is very high.

- **End-Organ Damage**—Other than the level of blood pressure, the most important risk factor is the presence of end-organ damage. Obviously, if the latter is present it is a sign that the hypertension is of sufficient severity to be producing progressive cardiovascular disease and is, therefore, an almost certain indication that the blood

pressure should be reduced. Unfortunately, end-organ damage is difficult to detect.

The presence of minor changes in the optic fundi such as arteriolar narrowing, tortuosity, increased light reflex, irregularity and segmental spasm are occasionally seen in the optic fundi of normal persons. Furthermore, these changes are difficult to determine with certainty and there is often disagreement even among experts. Nevertheless, the presence of tortuosity, narrowing, and increased light reflex is often not very difficult to recognize with practice. Their presence should raise the suspicion of vascular changes and should be an additional element that can be added to the total clinical picture with the realization that the assessment is not 100% reliable. A fundusoscopic vascular change that is more easily identified and, hence, more reliable is the presence of arteriovenous nicking. As the arteriolar wall becomes thickened and hardened by secondary arteriolosclerosis, the vein wall is compressed and indented at the point of arteriovenous crossing. Such arteriolosclerotic changes can occur in normal individuals near the point where the vessels emerge from the optic disc, but if A-V nicking is found more peripherally than 2 disc diameters from the nerve head it is fairly reliable indication that the arterioles have become sclerotic as a result of hypertension. The more florid changes of striate hemorrhages, "cotton wool" exudates and papilledema are found only in severe or malignant hypertension.

Another clinically important sign of end-organ damage is left ventricular hypertrophy as determined by ECG. The manifesta-



The Eye and Mild Hypertension—Fundusoscopic vascular changes noticed in mild hypertension are arteriovenous nicking (two disc diameters peripherally from optic disc), arteriolar narrowing, tortuosity, increased light reflex and segmental spasms.

tions of LVH (see page 63) include increased voltage and ST-T changes. When both are present, it is a fairly reliable indication that left ventricular enlargement is present. The presence of voltage changes alone or ST-T changes alone are not as reliable, since they may be found in normal individuals. The earliest sign of left ventricular enlargement probably is an increase in voltage. Therefore, this is the most likely ECG finding to be seen in patients with mild hypertension who are developing myocardial hypertrophy. Increased voltage is a particularly useful finding if prior ECGs in the same patient show normal voltage. Apart from the consideration that increased voltage or even ST or T wave changes may be seen in normal individuals or may be due to other causes, they still represent important prognostic signs and, depending on the total clinical picture, should weigh heavily in favor of treatment.

Unfortunately, there are very few other



Proteinuria is a useful sign when present but it is rarely found in mild hypertension. If it does occur, an underlying renal disease should be suspected.

useful evidences of end-organ damage that can be detected clinically. Cardiomegaly by chest x-ray is difficult to be certain of because cardiac diameter is influenced by the height of the diaphragm, which in turn depends on body habitus and the depth of inspiration taken by the patient during the exposure of the film. Definite cardiomegaly as determined by x-ray usually is not seen until the patient begins to develop heart failure. Proteinuria is a useful sign when present but it is rarely found in mild hypertension. If it does occur, an underlying renal disease should be suspected.

• **Lability of the Hypertension**—Another most important determinant of risk is the lability of the blood pressure. A number of studies have indicated that mortality rates in patients whose blood pressures fall to normal under basal conditions such as hospitalization have only one-third to one-fourth the long term mortality of patients who remain hypertensive. Using a portable recording blood pressure apparatus, Sokolow found that many patients exhibit considerably lower blood pressures in their daily activities than they do in the doctor's office, but others do not. The former patients exhibited less evidence of end-organ damage and had fewer cardiovascular complications than the patients with the more persistently elevated blood pressure.

Sokolow's study is of importance because it demonstrates that many patients carry considerably lower blood pressures during their daily activities than they manifest in the physician's office. As a result, they are at considerably lower risk than the physician estimates. The identification of such

patients requires special techniques, the most valuable of which is home recordings of blood pressure or else frequent visits to the physician's office, preferably to see the nurse rather than the physician, for blood pressure checks. It is not difficult to teach a member of the family to record blood pressures in the home twice daily for a period of one or two weeks. Several spare blood pressure apparatuses can be kept in the office to be loaned out for this purpose and the office nurse can instruct the family member in how to take the pressure recordings.

While home recordings are ideal, they usually are not essential and the physician can arrive at an estimate of lability if he insists upon at least three office visits before embarking on a course of treatment. If the visits are closely spaced, no more than two weeks apart, the patient with labile hypertension frequently will reveal a normal pressure on one or more of these visits.

• **Level of Systolic Blood Pressure**—Prognosis is related to the level of systolic as well as diastolic blood pressure. In the Veterans study, prognosis was worse and the effectiveness of treatment was decidedly better in the patients with systolic blood pressures averaging 165 mm Hg or higher over several clinic visits than in patients with lower pressures as compared to control patients with similar levels of blood pressure.

• **Family History** — Severe hypertension often runs in families. If the patient is below age 45 and tells you that one or both parents died of a hypertensive complication, the patient's risk of developing a more

severe degree of hypertension in the future is increased. If he is not treated, the patient should at least be conscientiously followed.

● **Hypercholesterolemia or Diabetes Mellitus**—The presence of hypercholesterolemia or diabetes mellitus further increases the risk of myocardial infarction and peripheral vascular disease. Although there is no conclusive evidence presently available to indicate that antihypertensive treatment will be effective in reducing the risk of atherosclerotic complications, it would seem prudent in a patient with both hypertension and hypercholesterolemia to try to reduce both risk factors.

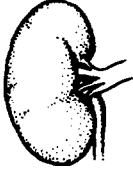
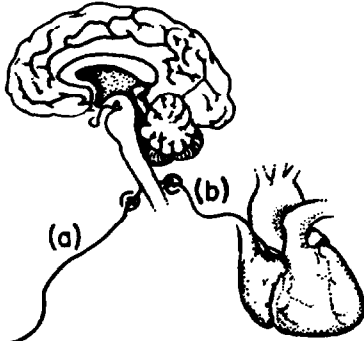
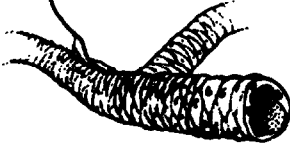
If a patient with a diastolic blood pressure averaging between 90-104 mm Hg has a number of the other risk factors listed above, the physician would be inclined to treat even though "solid" evidence of benefit is still lacking. A young male showing LVH on the electrocardiogram is at such high risk that most physicians would choose to treat him. On the other hand, in a 55-year-old white female with no signs of end-organ damage, treatment could be postponed. In the latter case, the expense and inconvenience of treatment and the possible induction of side effects outweighs the questionable benefits to be expected from treatment. It is well to remember also that in patients with mild hypertension there is no urgent need to begin treatment immediately. In cases of doubt, the physician can see the patient several times at six-month or yearly intervals to determine whether the process is progressive, stable or retrogressing.

Treatment

Although low-salt and weight-reducing diets have been advocated for the treatment of hypertension, this author has little confidence in their effectiveness. It is very difficult for most patients to make a permanent change in their dietary habits. Long-term followup studies in obese patients indicate that very few will maintain a reduced weight for more than a few years. Low salt diets are difficult to maintain when all canned and many processed foods are already salted. The average salt intake in the United States is said to be 10 grams per day. To reduce this appreciably requires special dietary foods and it is doubtful that even this will be sufficient to influence the hypertension appreciably. Experience with the dietary treatment of severe hypertension in the era before the advent of antihypertensive agents indicated that intake must be reduced to 200 mg of sodium or less to obtain an antihypertensive effect. Such a low intake required salt free bread and milk powder, as well as elimination of all canned goods and other commonly used foodstuffs. Tests of urinary sodium excretion indicated that the great majority of patients were not following the diet. It is much more acceptable to the patient and far more effective to simply prescribe a thiazide diuretic rather than to so seriously interfere with the patient's normal dietary habits. Some physicians have recommended modest restriction of sodium, but there is no evidence that lesser degrees of salt deprivation exert any antihypertensive effect.

In almost all patients with hypertension, long-term blood pressure control can only

Classes of Antihypertensive Drugs

Control Mechanism Affected	Drugs
1. Body sodium, plasma volume and extracellular fluid volume 	(a) Potassium losing diuretics: thiazides chlorthalidone loop diuretics (b) Potassium retaining diuretics: spironolactone triamterene
2. Sympathetic Nervous System 	(a) Alpha blockers phenoxybenzamine phentolamine (b) Beta blockers propranolol (c) Combined blockers reserpine alpha methyl dopa guanethidine clonidine
3. Arteriolar smooth muscle 	hydralazine diazoxide prazosin* minoxidil*

* Not yet approved by FDA

be achieved by using antihypertensive agents. The latter do not include sedatives or tranquilizers. Controlled trials comparing phenobarbital versus a placebo in benign essential hypertension have indicated that phenobarbital has no antihypertensive effects as compared to a placebo. The falls in blood pressure that physicians have observed with phenobarbital are actually due to a so-called "placebo effect."

• The Placebo Effect of Phenobarbital—

The placebo effect in hypertension can be explained on the following basis. Patients

often are apprehensive on their initial visit to the doctor's office and their blood pressure may then be raised above the usual level for them. If the patient is given a placebo and is then reexamined subsequently, the blood pressure often will be considerably lower or even normal simply because the patient is no longer apprehensive. When the physician prescribes a tranquilizer or sedative instead of a placebo, he concludes erroneously that it was the medication which reduced the blood pressure. Actually there is no harm during the

initial evaluation period to provide a small dose of a sedative or tranquilizer or even a placebo, providing the physician realizes that the effect he observed is not causally related to the medication. In all but severe hypertension, for properly classifying the severity of the hypertensive it is essential to have three or more office visits before initiating treatment. The levels obtained on the last two visits can then be averaged to obtain an index of the severity of the blood pressure elevation. You can omit the reading from the initial visit, because it is apt to be misleadingly high.

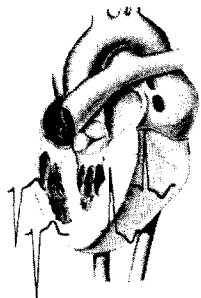
Another popular but dangerous misconception concerning treatment is that once the blood pressure is lowered it will remain at reduced levels without any further treatment. Permanent remission of hypertension is quite unusual. On the other hand, modification of the severity of the hypertension is quite common, but some form of treatment is still required. For example, it is often possible after six months or more of satisfactory blood pressure control to reduce the amount of medication required. If the patient had previously required several antihypertensive drugs in combination, it may be possible to gradually reduce and then omit all agents except one. Usually, the drug that is maintained is a thiazide diuretic. In general, however, the statement holds that "once a hypertensive always a hypertensive."

● **Antihypertensive Agents** — Antihypertensive drugs can be divided into classes according to their mode of action, which is to influence one of three blood pressure control mechanisms. The three control mecha-

nisms and the drugs which act upon them are shown in the Table.

An important, but poorly understood mechanism, involved in blood pressure control is the status of the extracellular fluid and plasma volumes. Expansion of these volumes leads to a rise of blood pressure and resistance to antihypertensive agents. Reduction of these volumes leads to opposite effects. Diuretics represent the basic antihypertensive medications because they not only reduce blood pressure in their own right but they also enhance the antihypertensive activity of any other drugs that might be added to the therapeutic regimen. A fuller explanation of their action is given below.

The sympathetic nervous system is primarily involved in the "flight or fight" reactions that were concerned with self preservation of primitive man. In this reaction, cardiac output and blood flow to voluntary muscle are greatly increased. The alpha adrenergic receptors produce arteriolar constriction to raise total peripheral resistance and venous constriction to increase venous return to the heart. The beta adrenergic receptors increase heart rate and ventricular contractility to elevate cardiac output and they also produce vasodilatation in muscle to raise muscle blood flow. In modern civilization, fear and anger activate this adrenergic reaction, usually without an overt flight or fight response. The sympathetic system also is involved in reflex adaptive responses such as to postural changes and temperature alterations. Also, at rest, the system is more active when we are awake than during sleep.



It is well to remember also that in patients with mild hypertension, there is no urgent need to begin treatment immediately.

As indicated above, the adrenergic receptors produce vasoconstriction of systemic arterioles and in veins, with the exception of those in voluntary muscle. Drugs which block this system alone are unsatisfactory for the long-term treatment of hypertension because they produce disturbing side effects, including orthostatic hypotension and tachycardia. The tachycardia occurs because the beta receptors remain active and the fall in blood pressure is detected by the baroreceptor nerves of the carotid sinus and aortic arch, which in turn activate the cardiac sympathetics.

The beta adrenergic receptors control blood pressure primarily by increasing cardiac output and drugs which block these receptors act by reducing cardiac output. These drugs are rather weak antihypertensive agents but they have the advantage of being relatively free of disturbing side effects. Antihypertensive drugs which block both alpha and beta receptors are more effective antihypertensive agents. Reserpine, alpha methyl dopa or clonidine and guanethidine all act at different sites in the sympathetic nervous system and different patients may respond best to one or another of these compounds. Also, the severity of the side effects such as orthostatic hypotension varies with each one of these drugs.

The intrinsic tone of the arteriolar smooth muscle appears to be controlled primarily by the nutritional needs of the tissues. For example, high oxygen concentration in a given tissue site leads to local vasoconstriction and vice versa. A drug which reduces the tone of arteriolar smooth muscle will result in a reduced response to

all vasoconstrictor stimuli including humoral, neurogenic and local influences. The result is a fall in peripheral resistance. Vasodilator agents, such as hydralazine, affect the resistance vessels primarily rather than the veins. They therefore do not produce peripheral pooling of blood volume and resulting orthostatic hypotension.

• **Compensatory Reactions Elicited by Antihypertensive Agents** — Reduction of blood pressure with a drug affecting one mechanism often initiates compensatory reactions involving the other mechanisms. For example, reduction of blood pressure with a sympathetic blocking drug leads to salt and water retention by the kidney. The resulting expansion in extracellular volume tends to negate the antihypertensive effects of the sympathetic blocker. Reduction of blood pressure with a vasodilator drug such as hydralazine causes both salt and water retention and reflex activation of the sympathetic system via the baroreceptors. The latter results in an increase in heart rate and cardiac output which partially restores the hypertension. Only the diuretics appear to be relatively free of eliciting compensatory responses, which is an additional reason for selecting a thiazide as the primary medication in mild or moderate hypertension.

• **Diuretics**—The antihypertensive effect of a thiazide diuretic is dependent upon the production of a sufficient loss of body sodium and water to deplete the extracellular fluid volume including the plasma volume of several liters of fluid. The reduction in volume occurs within the first 48 hours of continuous effective treatment, following which compensatory mechanisms come into

play to prevent any further loss of extracellular fluid. The volume depletion is fairly well maintained for as long as the diuretic is continued. If the latter treatment is withdrawn the volume loss is restored over a period of 24 to 48 hours.

The thiazides and related diuretics have a built-in safety margin because the extent of the volume depletion is limited and elevation of dosage above the therapeutic range fails to induce any further loss of extracellular fluid. This safety factor is not present with the loop diuretics, furosemide and ethacrynic acid. The diuretic effectiveness of the latter compounds increases with increasing doses so that it is possible to produce dangerous volume depletion with large doses of the latter. An additional disadvantage of the loop diuretics in long term management is that the duration of the diuretic effect is short, requiring four or more doses per day to maintain the volume depletion.

The thiazide diuretics becomes ineffective in the presence of severe renal failure because their diuretic activity begins to fall off with reduced glomerular filtration rates and essentially stops when the latter reaches about 20 ml/min. A diuresis still may be obtained, however, in some patients with renal failure if large doses of the loop diuretics are administered. Renal failure is about the only instance where furosemide or ethacrynic acid are indicated in the treatment of chronic hypertension.

Because the volume depletion should be maintained in patients with hypertension, an intermittent dosage schedule for administering the thiazide diuretics usually is unsatisfactory. Furthermore, the long acting

agents are preferred over the shorter acting, since with long-term use, once or twice per day medications result in better compliance and adherence on the part of the patient than three or four times per day dosage schedules.

The most common side effects produced by the thiazides and related compounds or by the loop diuretics are hypokalemia, hyperuricemia, and hyperglycemia. The hypokalemia is secondary to the volume depletion since the latter stimulates the production of renin and aldosterone. The hypokalemia usually is mild and requires no treatment except in patients who are receiving digitalis. In the latter cases, hypokalemia must be prevented by administering a potassium-retaining diuretic such as spironolactone or triamterene. Fixed dose combinations in which the potassium-retaining diuretic is combined with hydrochlorothiazide are both effective and convenient (Aldactazide® or Diazide®).

Hyperuricemia secondary to thiazide diuretics occurs in approximately half of the treated patients. In individuals predisposed to gout, especially patients with renal impairment, acute gout will be precipitated by administration of thiazides. The acute attack of gout should be treated with colchicine and the patient placed on probenecid if renal function is good or on allopurinol if renal failure is present. The thiazide diuretics should not be discontinued. Asymptomatic hyperuricemia secondary to thiazides requires no treatment and rarely, if ever, is a cause of secondary gout.

Thiazides and related diuretics diminish glucose tolerance, presumably due to inter-



Although low-salt and weight-reducing diets have been advocated for the treatment of hypertension, this author has little confidence in their effectiveness.

ference with release of insulin from the pancreas. The hyperglycemia is mild and usually requires no treatment. If there is glycosuria, a diabetic diet is indicated or if acidosis occurs (a rare event) the patient should be given insulin. It is rarely necessary or desirable to discontinue the thiazide diuretics because of changes in carbohydrate metabolism.

On rare occasions a patient taking thiazide treatment will suddenly develop severe hyperglycemia with blood sugar levels in excess of 400 mg% accompanied by glycosuria but not by ketoacidosis. Severe dehydration can occur, however, with hyperosmolality of the plasma. The offending agent should be discontinued, although it is sometimes possible to begin treatment again after several weeks, preferably with a chemically unrelated diuretic such as chlorthalidone to replace hydrochlorothiazide or vice versa.

Although quite uncommon, the thiazides may induce sensitivity reactions. Such reactions include erythema multiforme, thrombocytopenic purpura, leukopenia, aplastic anemia and pancreatitis.

All thiazides and related diuretics, such as chlorthalidone, exert similar effects. The only differences among these compounds is the level of the effective dose and the duration of action. In older patients, it is advisable to begin with a small dose and increase if necessary, but most patients respond best if they are given full therapeutic doses such as 50 mg of hydrochlorothiazide twice daily or chlorthalidone 50 to 100 mg once daily.

The potassium-retaining diuretics, spi-

ronolactone and triamterene, are not satisfactory for the treatment of hypertension when they are used as the sole diuretic medication because in therapeutic doses they do not cause sufficient sodium loss and resulting reduction in volume. They are, however, useful in combination with thiazides in patients in whom it is important to avoid hypokalemia. Such combinations, including the available fixed-dose combinations, cause a satisfactory reduction in volume without inducing hypokalemia. These combinations are more satisfactory and better tolerated than potassium-replacement therapy, which is not a very reliable method for normalizing thiazide-induced hypokalemia.

• **Reserpine**—Reserpine is an effective, inexpensive and convenient form of medication, but it is also a potentially dangerous drug since it can induce severe emotional depressions. The drug can be given reasonably safely if the patient is warned of the possibility of depression and if the drug is discontinued promptly before the depression becomes well established.

Reserpine depletes the catecholamine stores in the sympathetic nerve endings. Sympathetic nerve responses are not completely blocked but they are considerably reduced. Both alpha and beta adrenergic nerves are affected at a dose of 0.25 mg daily of reserpine and the sympathetic inhibiting effect becomes manifest after one week. The action of the drug is very prolonged; after discontinuing reserpine, evidences of catecholamine depletion may persist for a one or two week period.

Because of the incomplete depletion of catecholamines, reserpine interferes only

mildly with sympathetic vasoconstrictor reflexes and, as a result, orthostatic hypotension is rarely seen. There is a mild bradycardia. The effect in the brain is to induce a mild tranquilizing action, which in some patients becomes a disturbing lethargy and in few goes on to a frank depression.

As an antihypertensive agent, reserpine alone seldom is effective. However, it is effective in a high percentage of patients with mild and moderate hypertension when given in combination with a thiazide diuretic. The therapeutic dose is 0.2 or 0.25 mg daily. Further increases in dosage leads to little or no further antihypertensive effect but may induce more frequent and disturbing side effects. Therefore, there is little need to modify dosage and fixed dose combinations of a thiazide or related diuretic with reserpine are advisable, both for convenience and expense.

The most important side effect of reserpine is emotional depression. This reaction may be difficult to recognize. The leading manifestations are melancholia, loss of self confidence, early morning awakening, loss of libido, and reduced appetite. A more common and less severe reaction to reserpine is lethargy and loss of drive, without the development of a true depression.

The most frequent side effect of reserpine is nasal stuffiness. The symptom is usually most troublesome at night. Local application of nasal decongestents can be used at bedtime if the condition is not very severe. If the condition is quite troublesome, the daily dose of reserpine can be reduced in half. Patients who have nasal stuffiness should be told to discontinue reserpine tem-

porarily when they have a head cold or if they develop persistent epistaxis.

Because of the sympathetic inhibition, patients taking reserpine often manifest signs of parasympathetic hyperactivity. This may result in bradycardia, increased appetite due to increased hunger contractions of the stomach and an increased frequency of bowel movements. There may also be increased gastric acidity, but experience does not indicate a significant increase in gastric ulceration in reserpine-treated patients. Male patients may complain of impotence while taking reserpine.

Recently, it has been reported that reserpine usage is associated with an increased incidence of carcinoma of the breast in postmenopausal females. Further investigations will be required to establish the validity of this observation. Until this is done, however, it would seem wise to avoid initiating the use of reserpine in women, although it can be given safely to men. Hypertensive women whose blood pressures are presently well controlled with reserpine probably should not have the drug discontinued until such time as additional evidence becomes available.

● **Alpha Methyldopa**—The mode of action of alpha methyldopa is at present unclear. The most recent evidence suggest that it acts centrally to suppress the activity of the sympathetic nervous system in the region of the hypothalamus or vasomotor centers. As with reserpine, the sympathetic reflex responses are only mildly inhibited and orthostatic hypotension is uncommon. The reduction of blood pressure is associated with a decrease in total peripheral re-

sistance, while cardiac output remains essentially unchanged. Alpha methyldopa or its active metabolic products seem to be excreted in the kidney. In patients with renal failure, the drug is retained, which causes a cumulative antihypertensive effect with continued administration of the drug.

Alpha methyldopa, like reserpine, is much more effective if it is given with a thiazide diuretic. The initial dose of alpha methyldopa is 250 mg twice daily. Although the drug usually is given four times daily, there seems to be no reason for this as the duration of action of the drug is quite long. The doses are then titrated upward at succeeding office visits until there is a satisfactory antihypertensive effect or disturbing side effects or until a dose of 1000 mg twice daily is reached. Increase of dosage beyond this point exerts little if any additional antihypertensive effect and becomes both expensive and awkward for the patient to take.

The important toxic effects of alpha methyldopa are hepatitis and hemolytic anemia. The hepatitis rarely is severe. It characteristically appears during the first six weeks of treatment and is heralded by low grade fever and elevation of SGOT. The patients do not usually develop jaundice. Alpha methyldopa induces a positive Coombs in about 10 to 20% of patients and in rare instances this leads to a hemolytic reaction with resulting anemia.

Less severe but more frequent side effects of alpha methyldopa include sleepiness and dryness of the mouth. The former is most troublesome in patients who work at a desk, because the sleepiness is more common

when the patients are physically inactive.

● **Hydralazine**—Hydralazine is a vasodilator drug acting directly on arteriolar smooth muscle; it has no sympathetic blocking activity. Because the sympathetic nervous system is not inhibited, the fall in blood pressure produced by hydralazine is antagonized by the baroreceptors which reflexly induce an increase in heart rate and cardiac output over the sympathetic nervous system. This adverse reflex response must be combated by the administration of a sympathetic blocking agent such as reserpine or propranolol. Also, because the fall in blood pressure induces fluid retention, hydralazine usually must be given in conjunction with a thiazide diuretic. Thus, hydralazine represents a third order antihypertensive agent. It is most useful in patients whose blood pressures do not respond satisfactorily to a combination of a thiazide plus reserpine, or thiazide plus alpha methyldopa.

Although the duration of action of hydralazine is only about six hours, the drug is used primarily as an adjunct to other longer acting drugs in providing an additional downward kick to the blood pressure. For this purpose it can be effectively administered only twice or three times daily. The initial dose is 25 mg twice daily, which is increased to three times daily if needed. Additional dose increments are 50 mg twice daily and finally, 50 mg three times daily. Further increases in dose are not advisable because of the possibility of inducing the lupus syndrome, which is dose-related. Although the manufacturer makes a 10 mg tablet, this dose is too low in most patients.

The most important side effect of hydralazine is the development of a syndrome resembling disseminated lupus except for the absence of renal involvement. Fever, dermatitis, and arthritis are prominent clinical features and the presence of lupus cells and antinuclear antibodies in the blood are the most diagnostic laboratory features. The manifestations of lupus promptly subside when the drug is discontinued. The lupus reaction is seldom, if ever, seen if the daily dose of hydralazine is kept below 300 mg per day.

A frequent and disturbing side effect of hydralazine is headache, which probably is due to cerebral arterial vasodilatation. The frequency and severity of the headache is minimized when hydralazine is added to a diuretic-sympathetic-blocker combination and when the doses are increased gradually. Other side effects such as palpitations, angina, and dyspnea on exertion are related to the reflex cardiac stimulation and are largely prevented by drugs which inhibit the beta-adrenergic system.

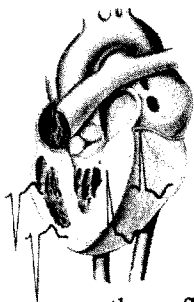
● **Propranolol**—Beta adrenergic blocking agents have recently become quite popular in Europe for the treatment of essential hypertension. The only drug of this type available in this country at the present time is propranolol, but it has not yet been approved by the Food and Drug Administration for the treatment of hypertension. Propranolol lowers blood pressure primarily by reducing cardiac output. The beta adrenergic blocking action reduces myocardial contractility and heart rate which in turn leads to the reduction in cardiac output.

The dose of propranolol required in treat-

Therapeutic Principles in Managing Hypertensive Patients

- Use the blood pressure and the side effects to guide dosage adjustment.
- Each patient represents an individual therapeutic experiment. Maintain flexibility in choice of drugs and doses.
- Office or clinic readings of blood pressure can be misleading guides in some patients. "Escape" from the antihypertensive effects of the drugs can occur in apprehensive patients. Use home blood pressures when in doubt.
- The most common cause of treatment failure is lack of adherence. The causes for noncompliance are many and include the following:
 1. The patient was not properly informed of the importance of preventive treatment. The patient did not understand the nature of his illness or the need for continued treatment.
 2. The regimen was overly complicated with several different drugs being used, each with a different dose schedule.
 3. The patients were not contacted when they failed to keep appointments.

ing hypertension often is much higher than is used in other conditions. The initial dose is 20 mg three times daily and this is increased as needed to 40, 60, 80, 100 and 120 mg three times per day. Doses as high as 1 to 2 grams have been used in Europe for treating severe hypertension. In order to minimize the dose requirement, it is advisable to administer a thiazide as a background medication. A rational and useful combination of antihypertensive agents is propranolol and hydralazine. In this case, the propranolol is used primarily to prevent



It is . . . far more effective to simply prescribe a thiazide diuretic rather than to so seriously interfere with the patient's normal dietary habits.

the reflex increase in heart rate and output induced by the vasodilator drug. Smaller doses of propranolol, such as 40 mg 3 times daily, will accomplish this purpose.

The great advantage of propranolol is that it is relatively free of disturbing side effects. There is no orthostatic hypotension and no sexual impotence. Propranolol is contraindicated in patients with recent congestive heart failure, bronchial asthma and in insulin dependent diabetes. It should be used with caution in patients with intermittent claudication.

Practical Considerations in Treatment

In patients with mild hypertension, the so called "step care" method of treatment is used. Patients are first given a thiazide diuretic, then if necessary a sympathetic blocking agent is added, and finally a vasodilator drug. Thiazides alone in full diuretic doses, such as hydrochlorothiazide 50 mg twice daily, will control the blood pressure in approximately 50% of patients. In the remaining patients, the thiazide will enhance the antihypertensive effects of other drugs. On the other hand, if the blood pressure is reduced on thiazide alone and the patient is complaining of hypotensive side effects such as weakness, fatigue, or faintness, the dose of the diuretic is reduced.

If the patient has received full doses of thiazides and the blood pressure remains elevated, the therapist may add either reserpine, alpha methyldopa, or propranolol. Depending on the response, each of these agents may be administered in succession until one is found which is both effective and well tolerated. Such combinations of a

thiazide and a sympathetic blocking drug should control the hypertension in an additional 30% of patients. In the remainder, hydralazine is added.

Despite the best therapeutic effort, there will remain 20 or 30% of patients whose hypertension is incompletely controlled. However, even partial reduction of blood pressure appears to be effective in preventing major hypertensive complications. The experience of the Veterans Study indicated that the incidence of complicating events was not significantly different in the patients whose diastolic blood pressures averaged about 95 mm Hg during treatment, as compared to those whose diastolic levels were reduced below 80 mm Hg.

Elderly patients may become quite tired and lethargic from reserpine or alpha methyldopa. In such patients, a thiazide plus hydralazine may be effective. Elderly patients are less apt to show a reflex tachycardia from hydralazine than do younger patients, and the risk of inducing angina with hydralazine is small when it is given in combination with a thiazide diuretic. Elderly patients also may need only half doses of thiazide diuretics.

Some patients under treatment manifest considerably higher levels of blood pressure in the doctor's office than they do during their normal daily activities. Since the physician is guided only by these misrepresentatively high readings, the doses of the antihypertensive agents may be raised to the point where the patient experiences hypotensive symptoms. If adequate doses of antihypertensive agents have been administered without apparent effect on the office read-

ings of blood pressure and if the patient complains of such symptoms as weakness, faintness and excessive fatigue, the physician should suspect that the office readings are not representative. In such cases, the use of home readings of blood pressure are very useful. Home blood pressure recordings provide a much more representative response to the drug therapy and the physician may find that an actual reduction in dosage is indicated.

Patients with mild hypertension are asymptomatic and the antihypertensive agents they are given may make them feel worse than they felt previously. Therefore, every patient who embarks on a course of treatment for hypertension should receive some indoctrination into what hypertension is, what it does, and what treatment is supposed to accomplish.

There are available today a variety of antihypertensive agents the proper choice of which will result in the satisfactory control of hypertension in the great majority of patients. The ability to achieve such con-

trol represents a great therapeutic advance, since it is now known that control of the elevated blood pressure affords protection against the principle complications associated with hypertensive cardiovascular disease. ◀

References

1. National Health Survey: Hypertension and Hypertensive Heart Disease in Adults. 1960-62, U.S. Dept. of Health Education and Welfare, Vital and Health Statistics, Series II, No. 13, U.S. Government Printing Office, 1966.
2. Pickering G: *High Blood Pressure*. 2nd ed., New York, Grune and Stratton, 1968.
3. Truete J, Cornfield J and Kannel WB: A multivariate analysis of the risk of coronary heart disease in Framingham. *J. Chron. Dis.* 20:511, 1967.
4. Goldstein M: Longevity and health status of whites and nonwhites in the United States. *J. Nat. Med. Assoc.* 46:83, 1954.
5. Hamilton M, Thompson EN and Wisniewski TKM: The role of blood pressure control in preventing complications of hypertension, *Lancet* 1:235, 1964.
6. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. I. Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. *JAMA* 202:1028, 1967.
7. Ibid. II. Results in patients with diastolic blood pressures averaging 90 through 114 mm Hg. *JAMA* 213:1143, 1970.
8. Freis ED: *Introduction to the Nature and Management of Hypertension*. Bowie, Md. Robert J. Brady Co., 1974.